2. ***The escitalopram NDA heart rate data and ECG ventricular rate data suggest that escitalopram and citalopram have a small but consistent bradycardic effect. For drugs that cause bradycardia, Bazett's correction for QT interval may minimize the degree of QT prolongation. We request that you repeat your QTc analyses following correction of the QT data using Fridericia's method (QT/cube root of RR interval). In addition, you may choose to calculate a correction factor based on your baseline or placebo data (see attached copy of division recommendation for QT correction) and apply it to the uncorrected QT.***

Forest Laboratories, Inc. reanalyzed QTc data. QTcB (Bazett's method) and QTcF (Fridericia's method) were used to adjust for heart rate. Table 1 summarizes results of the reanalysis.

Table 1. Descriptive Statistics of QTc by Treatment Group, Clinical Studies SCT-MD-01, SCT-MD-02, 99001, and 99003

ECG Parameter		Placebo (N=592)	Escitalopram (N=715)	Citalopram (N=408)
Sample Size (N)		540	650	367
QTc Mean Screening	QTcB	385.1	385.7	388.3
	QTcF	377.1	378.6	380.5
QTc Mean Endpoint	QTcB	385.9	387.7	389.9
	QTcF	377.5	382.5	384.2
QTc Mean Difference*	QTcB	0.8	2.0	1.6
	QTcF	0.4	4.0	3.7
LSM (SE) for Change from Baseline **	QTcB	1.1 (0.83)	1.8 (0.76)	1.7 (1.05)
	QTcF	0.6 (0.72)	4.0 (0.66)	3.7 (0.91)

* Endpoint-Screening.
** Least squares means were obtained from the ANCOVA model with treatment and study as factors and baseline value as covariate.

Forest Laboratories also provided graphic data of Correlation Coefficient for Escitalopram S-CT Plasma Concentration and Change from Baseline to Endpoint in QTc Safety Population (Sponsor Table 1 through table 6) for study SCT-MD-01. The correlation coefficients were not significant. The sponsor did not provide similar data for other 3 clinical studies, SCT-MD-02, 99001, and 99003. The sponsor did not provide a protocol for correlation study.

3. ***In Attachment 5 of the September 27, 2001 submission, Table 1 lists the patients with normal screening ECGs and ECGs at endpoint.***

   Please provide your definition of the terms "QTcB dispersion prolonged" and "QTcB dispersion increased"

   QTcB dispersion prolonged and QTcB dispersion increased were used interchangeably and included cases with QTcB dispersion>100ms and /or >100% increase in dispersion.

Certain of these abnormality descriptions are marketed as "clinically significant". What were the criteria for clinical significance?

There were no set criteria for clinical significance, and the assessments were based on the judgment and interpretation of the central cardiologist and/or the site investigator evaluating the ECG.

Table 2 "Incidence of ECG Abnormalities (>= 1% in active treatment group) at Endpoint" appears to have been mistakenly left out of the archival and desk copies of the submission. Please include this table in the new submission. It would be useful if you only included treatment emergent ECG abnormalities. Please also include the incidence of ECG abnormalities among the active control and placebo control groups.

The sponsor presented the incidence rates by treatment group in table 12 of this submission.

4. Please submit a discussion of any postmarketing reports that you have received describing QT or QTc prolongation, torsades de pointes, ventricular tachycardia, or ventricular arrhythmia associated with citalopram therapy. Include the original reports as well

The sponsor provided a postmarketing report dated January 9, 2002 and I will discuss the report in next section of this review.

3. A Description of the Technical Problems with ECG Recording Identified by CDER's Division of Scientific Investigation

On May 21, 2002, Dr. Ni Khin, of the Division of Scientific Investigation (DSI), alerted DNDP that during the inspection of study SCT-MD-03 site 06 (Dr. Doraiswamy), duplicates of ECGs had been identified. The FDA inspector found identical ECG tracings in the records for different patients. A review of the ECG procedures revealed that the equipment provided by the central ECG laboratory did not always function as intended, which infrequently resulted in the replacement of a patient's ECG recording with that of the previously recorded ECG. The ECGs that had been replaced by a prior recording were not recoverable. On June 29, 2002, DNDP also received an investigation summary from DSI concerning the ECG data (included as Appendix 2).

The same ECG transmission equipment provided by this laboratory was also used in Studies SCT-MD-01 and SCT-MD-02. Forest laboratories reexamined all ECG tracings for all patients screened and enrolled in Studies SCT-MD-01, SCT-MD-02, and SCT-MD-03. A total of 45 duplicate tracings were identified at 14 of the 35 sites that participated in Study SCT-MD-01, and a total of 34 duplicate tracings were identified at 8 of the 22 sites that participated in Study SCT-MD-02.

The ECG data from Studies SCT-MD-01 and SCT-MD-02 were reanalyzed after excluding all data derived from the duplicate tracings. The data for a total of 54 patients with duplicate baseline and/or follow-up ECGs (13 placebo, 25 escitalopram, 16 citalopram) were excluded from the quantitative analyses of ECG parameters. In Study

SCT-MD-01, 32 of 419 (7.6%) patients were excluded from the analyses. In Study SCT-MD-02, 22 of 333 (6.6%) patients were excluded from the analyses.

At the request of DNDP, Forest submitted the results of their reanalysis of the unduplicated ECGs to FDA (submission dated May 28, 2002). Table 2 presents the original and revised analysis of pooled studies SCT-MD-01, SCT-MD-02, 99001, and 99003, that was originally included in the Safety Update to NDA # 21-323 submitted on July 12, 2001. (Studies 99001 and 99003 were not affected by the US central ECG laboratory.) Table 2 also presents analyses similar to those submitted on December 18, 2001, including unadjusted and adjusted mean values of the change from baseline in QTcF (Fridericia's method).

Table 2 ***Mean Changes in ECG Parameters Safety Update***

ECG Parameter	*Placebo (N=592)*		*Escitalopram (N=715)*		*Citalopram (N=408)*	
Heart Rate	540	0.3	650	-2.3	367	-2.4
	527	**0.3**	**625**	**-2.2**	**351**	**-2.7**
QRS Interval	540	0.0	650	0.6	367	0.0
	527	**0.0**	**625**	**0.5**	**351**	**0.1**
PR Interval	540	0.6	648	0.3	366	-0.6
	527	**0.3**	**623**	**0.6**	**350**	**-0.5**
QT Interval	540	-0.2	650	7.5	367	7.6
	527	**-0.0**	**625**	**7.4**	**351**	**8.2**
QTcB Interval (Bazett)	540	0.8	650	2.0	367	1.6
	527	**0.9**	**625**	**1.9**	**351**	**1.2**
Adjusted QTcB Interval (Bazett)	540	1.1	650	1.8	367	1.7
	527	**1.5**	**625**	**1.9**	**351**	**1.5**
QTcF Interval (Fridericia)	540	0.4	650	4.0	367	3.7
	527	**0.5**	**625**	**3.9**	**351**	**3.7**
Adjusted QTcF Interval (Fridericia)	540	0.6	650	4.0	367	3.7
	527	**0.9**	**625**	**4.1**	**351**	**3.7**

Revisions are indicated in bold.
Adjusted QTc intervals are the least squares means obtained from the ANCOVA model with treatment and study as factors and baseline value as covariate.

There were no changes in the incidence of potentially clinically significant (PCS) values of the ECG parameters. The percentage of patients in the safety update database with an

overall ECG interpretation of normal or abnormal at baseline and follow-up, original and revised, are shown in Table 3.

Table 3. Incidence of ECG Abnormalities Safety Update

Screening	*Endpoint*	*Placebo n/ N (%)*	*Escitalopram n/ N (%)*	*Citalopram n/ N (%)*
Normal	Normal	440/537 (81.9)	509/644 (79.0)	288/364 (79.1)
		428/524 (81.7)	**485/619 (78.4)**	**274/348 (78.7)**
Normal	Abnormal	35/537 (6.5)	42/644 (6.5)	25/364 (6.9)
		34/524 (6.5)	**41/619 (6.6)**	**25/ 348 (7.2)**
Abnormal	Normal	24/537 (4.5)	36/644 (5.6)	17/364 (4.7)
		24/ 524 (4.6)	**36/ 619 (5.8)**	**15/ 348 (4.3)**
Abnormal	Abnormal	38/537 (7.1)	57/ 644 (8.9)	34/ 364 (9.3)
		38/ 524 (7.3)	**57/ 619 (9.2)**	**34/ 348 (9.8)**

Revisions are indicated in bold.

In conclusion, the revised analyses after excluding the data derived from the duplicate tracings yielded results very similar to those previously submitted in the NDA and safety update. However, there is no way to know what the missing data from the 13 placebo, 25 escitalopram, and 16 citalopram patients whose ECGs were lost would have shown.

4. Post-Marketing Review of QT/QTc Prolongation, Torsades de Pointes, Ventricular Tachycardia, Ventricular Arrhythmia and Citalopram Therapy

Forest Laboratories submitted a Post-Marketing Review of QT/QTc Prolongation, Torsades de Pointes, Ventricular Tachycardia, Ventricular Arrhythmia associated with citalopram therapy for the period of July 1, 2000 through November 30, 2001. The report was based on Forest Laboratories' safety database. In this submission, Forest Laboratories also provided a report, Lundbeck Report number 72/345 entitled "An Updated Survey of QT Prolongation and Torsade de Pointes Arrhythmia. Citalopram in Therapeutic Doses and Overdose" prepared by Forest Laboratory's licensing partner H. Lundbeck A/S, Denmark dated 22 December 2000. I also requested FDA citalopram post-marketing data from Office of Drug Safety, FDA.

4.1 Post-Marketing review, The Forest Laboratories' Safety Database, July 1, 2000 through November 30,2001 and Post-Marketing review, MedWatch Database, Jan 1, 2000 through April 30,2002

Forest Laboratory's safety database identified 18 post-marketing cases for the period of July 1, 2000 through November 2001 (Appendix 1). Fifteen of these cases are serious and three non-serious per Forest Laboratories. Among the serious cases, two deaths (S01-USA-00206-01 and S00-USA-0191301) were reported. Most patients were female patients (female:12, male:3, and unk:3). Ten cases described QT prolongation, three cases described torsades de pointes, four cases described syncope or seizure, and three cases described ventricular arrhythmia. Some cases described more than one condition.

ODS provided DNDP with 50 citalopram post-marketing adverse event reports. Sixteen cases are duplicates. Of the remaining 34 cases, all but five were included in the sponsor's report. Summary tables in Appendix 1 summarizing the cases who are included and not included in the Forest Laboratories' Safety Database.

4.1.1 Deaths

Case S01-USA-00206-01 was an U.S. spontaneous report received from a county medical examiner who reported that a 42-year-old female patient who had been receiving Celexa therapy died of unknown cause. While the patient was shopping with her husband, she had symptoms of intermittent chest pain and felt faint. The patient and her husband left the store and were driving in a car when the patient experienced what the medical examiner described as classic symptoms (almost seizure-like movements) of ventricular arrhythmia. Information on the dosing, duration, or indication for Celexa therapy was not known. The patient's husband reported that Celexa was the only medication the patient was taking. The medical examiner stated that the patient had a history of asthma and was a heavy smoker. Autopsy was not performed. The cause of death was unknown. The report speculated that the cause of death was ventricular arrhythmia.

Case S00-USA-01913-01 described a report from a Forest sales representative that a physician speaker for Eli Lilly was giving talks to other physicians claiming that in his practice, Celexa caused QT prolongation and death. No specific case information or physician contact information was provided.

4.1.2 Selected Serious Cases

Case S01-FRA-00062-01 is a serious case reported by a French cardiologist. A 51-year-old female developed QT prolongation, torsade de pointes, and syncope during citalopram therapy (20 mg po qd). During the therapy, the patient was hospitalized due to a loss of consciousness which resolved. ECG revealed QT prolongation of 533 msec and torsades de pointes; she was also noted to be hypokalemic (no value provided). Citalopram therapy was discontinued and QT values returned to normal (433 msec). Information about ECG measurement methods was not provided. Citalopram was restarted at 20 mg daily, and the QT value increased (value not provided). No concomitant medications were reported and the patient had no known cardiac history.

Case S01-NOR-00229-01 is a 24-year old Iranian female who experienced syncope, torsades de pointes, and ventricular tachycardia during citalopram therapy. It was reported that the patient had been in Norway for approximately ten months, during which time she initiated treatment with citalopram. Medical history included QT prolongation, with an ECG done in April 2000 showing a QTc of 540 msec. The patient started citalopram 30 mg daily on November 12, 2000. Two episodes of 'sudden syncope' on 11/20/00 and 11/27/00 were reported. The syncopal episode on 11/27/00 occurred 'while attached to an R-test' (a long-term ECG monitoring test) which showed fast ventricular tachycardia. On 11/27/00, the patient was admitted to a local hospital, the patient experienced several relatively short episodes of VT, and citalopram was discontinued on 11/28/00. On 12/01/00, the patient had VT for 2.5 minutes in conjunction with

cramps and syncope. The patient was electro-converted twice and had a temporary pacemaker placed. On 12/3/00, the patient was transferred to a central hospital, her condition stabilized and was discharged on 12/07/00 with a diagnosis of long Q-T syndrome and was readmitted to the local hospital (12/07/00 to 12/11/00). The patient showed no ventricular arrhythmia on readmission to the local hospital. The results of a 24-hour ECG done on 12/18/00 showed sinus rhythm with few ventricular extra systoles. No concomitant medications were reported..

Case S01-FIN-01644-01 is a 23-year-old male patient who experienced a grand mal seizure while receiving citalopram and buspirone hydrochloride. The patient was treated with citalopram 20 mg daily from 6/29/01 to 6/28/01, titrated to 40 mg daily on 6/29/01 to 6/30/01. The patient was also treated with buspirone 20 mg daily from 6/23/01 to 6/28/01. On 6/30/01 after titrating citalopram and buspirone to 40 mg daily, the patient experienced a grand mal seizure lasting three minutes. The patient was hospitalized on 6/30/01 and was discharged on the same day. An ECG that day showed a QTc interval of 488 msec. Citalopram and buspirone were both titrated back to 20 mg and continued at that dose. On a hospital summary received 9/3/01, the diagnosis of 'convulsions, NOS" after the use of citalopram and buspirone was reported.

Case S00-USA-01487-01 is an elderly female with a history of coronary artery disease and an implanted defibrillator. The patient developed ventricular fibrillation and ventricular tachycardia while taking citalopram. The patient initiated citalopram 20 mg daily and later increased to 20 mg BID (dates unknown). While on the higher dose, the patient's defibrillator went off 15-16 times. The patient was hospitalized with ventricular fibrillation and ventricular tachycardia. The patient was also taking Wellbutrin and Risperdal. All medications were discontinued and the events subsided.

Case S01-USA-02093-01 is a 62-year-old female who started citalopram on 7/9/01 at 20 mg daily. On an unknown date after starting citalopram, the patient had two episodes of syncope. On 8/2/01 ECG showed QT and QTc interval of 469 msec and 510 msec, respectively, with bigeminy. Baseline ECG prior to citalopram showed QT/QTc intervals as 412 msec and 480 msec. Citalopram was stopped on 8/2/01. On 8/8/01 the patient had a normal perfusion study, normal left ventricular function, no ischemia, a normal tilt table study, negative Holter monitor test and a normal signal-averaged ECG. The patient's concomitant medications include prednisone and Combivent for chronic obstructive pulmonary disease.

Case S00-UKI-01907-01 is a 58-year female patient with a history of hypertension and cardiovascular disorder who experienced ventricular tachycardia two to three hours after receiving one dose of citalopram 20 mg on 10/12/00. The patient was hospitalized and recovered after treatment with Verapamil. She had a history of carotid endarterectomy, hypertension, and cardiovascular disorder. Concomitant medicines were lisinopril, atorvastatin, aspirin, bendrofluazide, amlodipine, and thyroxine.

Forest Laboratories concluded that based on post-marketing review for the period July 1 2000 through November 30, 2001 and previous reports, the evidence does not suggest an association between citalopram therapy and QT or QTc prolongation, torsades de pointes, ventricular tachycardia, and ventricular arrhythmia at therapeutic doses or overdoses. Forest Laboratories also stated that their conclusion is consistent with the known safety profile of citalopram as reflected in the current labeling for citalopram.

4.2 Post-Marketing review, An updated Survey of QT Prolongation and Torsade de Pointes Arrhythmia, Citalopram in Therapeutic Doses and Overdose. H. Lundbeck Report., Up to June 30,2000

H. Lundbeck, a licensing partner of Forest Laboratories for citalopram, performed analyses on the cardiovascular safety of citalopram in therapeutic doses and overdoses,

focusing on cases reported as QT prolongation, torsade de pointes (TdP) arrhythmia, and syncope; they also evaluated the benefit-risk ratio in patients with concurrent cardiovascular diseases. Although it appears that the report covers the period up through June 30, 2000, it is unclear when the time period began.

H. Lundbeck concluded that in therapeutic doses, citalopram has a safe cardiovascular profile in humans and no cases of QT prolongation or TdP arrhythmia reported are related to the use of citalopram. H. Lundbeck also concluded that in overdose, there are a few post-marketing cases of QT prolongation that may be attributable to citalopram. H. Lundbeck stated following further analyses it appears more likely that the events are coincident with citalopram rather than caused by citalopram.

H. Lundbeck reported 25 QT prolongation cases with therapeutic doses, 22 QT prolongation cases with overdoses, 12 ventricular tachycardia/arrhythmia cases (nine of the 12 cases are TdP cases) with therapeutic doses, and two ventricular tachycardia/arrhythmia cases (one TdP) with overdose.

4.2.1 Review of selected serious cases

Case DKLU0980361(0): This is a female patient treated with citalopram 20mg/d from 07-Oct-97 initially. The dose was increased to 40 mg/d on November 4, 1997. The patient presented with QTc prolongation (490 msec), without other clinical symptoms. QTc interval had been borderline prior to treatment with citalopram (450 msec). Treatment was discontinued on November 26, 1997 and QTc interval returned to normal (402 msec); however, 13 days later the QTc was again borderline prolonged (462 msec). The patient was reported to have made a full recovery.

Case DKLU0990862 (0): This is a 65- year old male patient who was treated with citalopram 20 mg/d from November 1998 for depression. On April 9, 1999, the patient had ventricular tachycardia, lost of consciousness for 30 seconds to 1 minute and was "unwell" for 2 days prior to the event. Patient had no chest pain, shortness of breath or palpitations. Citalopram was discontinued in April, 1999 and the symptoms have not recurred. The patient started anti-arrhythmic treatment with amiodarone and no more ventricular tachycardia was reported. The patient has a history of 'peripheral vascular disorder', 'left ventricular dysfunction', and developing CAD.

Case DKLU0991392 (0): This 34-year old male patient was treated with citalopram 20 mg/d from January 15 1999 for depression. On February 19, 1999, the dose was increased to 30 mg/d. On May 26, 1999, the patient took an ECG. The ECG showed an increased QT interval (476 msec) and ST-T changes in the inferior leads. The patient denied complaints of syncope or other pertinent clinical symptoms. On April 13, 1999, citalopram was decreased to 20 mg/d. ECG performed on May 11, 1999 showed the QT interval had reduced (428 msec) with non-specific ST-T changes in the inferior and lateral leads. A left ventricular hypertrophy was suspected but no definitive diagnosis was made. Citalopram dose was increased back to 30 mg/d (date not known). No follow-up ECG was reported. ECG performed on December 21, 1998 showed the patient had a borderline high QT interval and sinus bradycardia prior to treatment with citalopram. The reported QT interval durations were not corrected for heart rate.

Case DKLU0991651 (0): This is an 85-year old female patient with a history of CAD and hypertension who was treated with citalopram 10 mg/d from Oct 26, 1998 for mixed depression and anxiety. On Oct 29, 1998, the patient experienced prolongation of QT interval. She was admitted to hospital on Oct 30, 1998 for shortness of breath, left arm pain and nausea. The patient was diagnosed with unstable angina. Citalopram was discontinued on Oct 30, 1999 and the symptoms resolved (unknown date). Treatment with venlafaxine was started and the patient is currently doing fine.

Case DKLU0991754 (0): This is an 84 year old female patient with a history of CAD and diabetes who was reported as experiencing 'ventricular fibrillation and prolongation of QT-interval'. This patient was started with citalopram 20 mg/d in June 1999. On September 13, 1999, the patient started treatment of ciprofloxacin for a urinary tract infection. The patient was hospitalized on September 18, 1999 for worsening of nausea and was treated with IM metoclopramide. On Sep 19, 1999 she experienced ventricular tachycardia and ventricular fibrillation. Resuscitation was performed and she was transferred to another hospital. On the same day, the patient experienced ventricular fibrillation. The QTc interval was reported 'over 600 ms', and the patient experienced repeatedly torsades de pointes. The patient received treatment with amiodarone and lidocaine. Ciproflocacin and glibenclamide were discontinued on Sept 19, 1999. Citalopram and desmethylcitalopram plasma concentrations were assayed and the results were within normal therapeutic level on Sept 20, 1999. The ventricular tachycardia abated on Sept 22, 1999. Citalopram was discontinued on Sept 23, 1999, following the resolution of the VT. The QTc prolongation was reported abated and the patient was reported recovered without sequelae.

Case DKLU1000032(0): This 60 year old male patient was treated with citalopram 100mg/d from January 7, 1997 to October 12, 1999 for depression. On October 8, 1999 the patient had developed a burning feeling which started in the mouth and spread to the rest of his body. He also had short periods of flushing. He hyperventilated and an ECG showed QT interval prolongation. He was treated with glyceryl trinitrate and diazepam. On October 12, 1999, citalopram level was found to above therapeutic level. The patient had been treated with citalopram before, and the doctor suspected the patient had been taking more than prescribed. On October 12, 1999, citalopram was stopped and the patient was reported to have recovered completely. This case was reported as an overdose case.

Case DKLU100051(0): This is a 14 year old female patient treated with citalopram (unknown dose) from March 1999 for depression. On April 10, 2000, the patient took an overdose of 20 tablets of citalopram 40 mg (total of 800 mg) and was brought to the emergency room. An ECG reading on April 10, 2000 showed QT prolongation. The patient was admitted to hospital and citalopram was discontinued. The patient was released and fully recovered on April 11, 2000.

Case DKLU1000737(0): This is a 40 year old female patient who was treated with citalopram 10 mg/d from March 29, 2000 for depression. On March 30, 2000, five hours after taking her first dose, she felt numbness, shortness of breath, headache and lightheadedness. On March 30, 2000, the patient was evaluated in the emergency room and a mild decrease in her blood pressure was observed (unknown values). Potassium level was within normal limits and ECG showed no changes. Her symptoms were thought to be a 'conversion reaction'. The patient was sent home. On March 31, 2000, a physician diagnosed the patient to have QT prolongation, a decreased potassium level and severe hypotension (70/50mmHg). The patient was admitted to hospital on March 31, 2000 and was discharged on April 3, 2000. Citalopram was discontinued on March 30, 2000. The patient was not restarted on citalopram therapy. The outcome of the event was not reported. The patient refused to consent to release her medical records. In contrast to the report of normokalemia at the March 30 emergency department visit, a laboratory test result included in the case report for that day shows hypokalemia (K=3.2).

5. Discussion

The sponsor's ECG analyses do not provide consistent evidence of an escitalopram-related effect on cardiac repolarization although the studies analyzed were not designed to carefully look for such a relationship. Physiological influence, such as meals, sleep, and others can affect baseline QTc measurements. It is recommended to take several QTc baseline measurements and use the mean as a baseline. Baseline measurements should be consistent among different clinical studies in a drug development. The use of

different baseline ECGs in different clinical studies in escitalopram development could potentially limit the ability to detect drug-related effects in these studies.

The sponsor conducted a correlation study concerning escitalopram plasma concentration vs. QTc changes on one of the four clinical studies. Information about methods and timing obtaining blood sample and ECG was not provided. I can not rule out the possibility of a dose-response relationship between escitalopram and QTc prolongation based on the information available. The sponsor should [redacted]

Problems in quality control and quality assurance in obtaining ECGs pose a potential threat to the integrity of the escitalopram clinical development program. FDA inspectors with follow-up by Forest Laboratories identified over 7% ECGs duplicates (exact ECG graphs as previous patient on the ECG machine). Data analysis after eliminating the duplicates resulted in similar results as the data analysis including the duplicates; however, there is no way to recover the ECG data lost from the patients whose data was replaced by the duplicates.

Questions that escitalopram (and citalopram) may have the ability to prolong the QT interval raised in the multiple dose clinical pharmacology study 98107 have not been fully answered due to the inconsistent baseline QTc measurements among studies, lack of serum citalopram data, and ECG duplications.

Post marketing citalopram data suggests that citalopram might have been related to the development of QT/QTc prolongation, torsades de pointes, and ventricular tachycardia/arrhythmia. Despite the difficulties assessing the relationship between the cardiovascular events and citalopram due to lack of information about background incidence rates and citalopram exposure, some individual case reports are very compelling that citalopram might have been related to the development of QT prolongation, torsades de pointes and ventricular tachycardia/ arrhythmia (sections 4.1.1, 4.1.2, 4.2.2).

6. Conclusions

1). The sponsor's ECG analyses do not provide consistent evidence of an escitalopram-related effect on cardiac repolarization. The use of different baseline ECGs in different clinical studies could potentially limit the ability to detect drug-related effects in these studies. Questions that escitalopram (and citalopram) may have the ability to prolong the QT interval raised in the multiple dose clinical pharmacology study have not been fully answered.

2). Problems in quality control and quality assurance in obtaining ECGs pose a potential threat to the data integrity of the escitalopram clinical development program.

3). Post marketing citalopram data suggests that citalopram might have been related to the development of QT/QTc prolongation, torsades de pointes, ventricular tachycardia/arrhythmia.

7. Recommendations

1). Change the following language to include QTc prolongation in the labeling.

Other Events Observed During the Non-US Postmarketing Evaluation of Celexa (citalopram HBr)

It is estimated that approximately [redacted] have been treated with Celexa since market introduction. Although no causal relationship to Celexa treatment has been found, the following adverse events have been reported to be temporally associated with Celexa treatment in at least 3 patients (unless otherwise noted) and are not described elsewhere in labeling: angioedema, choreoathetosis, epidermal necrolysis (3 cases), erythema multiforme, hepatic necrosis (2 cases), neuroleptic malignant syndrome, pancreatitis, serotonin syndrome, spontaneous abortion, thrombocytopenia, ventricular arrhythmia, QTc prolongation, torsades de pointes, priapism, and withdrawal syndrome.

2). The sponsor should follow DNDP's guidance to develop proper protocol to further study escitalopram and QTc prolongation, torsade de pointes, and ventricular arrhythmia.

Appendix 1 Reported Cases

Table 1 Reported Cases, Post-Marketing review, The Forest Laboratories' Safety Database,

Case Code	Age	Sex	Date of Event	Reporter	Diagnosis	Dosage	Duration	Outcome	History
S00-UKI-01907-01	58	f	10/12/00	MD	VT	20 mg qd	1 day	hospitalization	Cardiovascular disease; HTN
L01-USA-01339-01	21	f	unk	MD publication	QT +	400 mg overdose	unk	hospitalization	none
S01-USA-01623-01	unk	m	8/9/01	MD	QT + MI	200 pills	once	hospitalization	Suicide attempt
S00-USA-01913-01	unk	unk	unk	MD	QT + Death	unk	unk	Death?	unk
S01-USA-00206-01	42	f	2/8/01	Medical examiner	Death	unk	unk	death	asthma
S01-NOR-00229-01	24	f	?/?/00	MD	QT + Torsade	30 mg qd	unk	Life threatening	unk
S01-GER-01168-01	unk	f	?/?/01	MD?	Torsades Syncope No QT +	20 mg qd	60 days	Other???	CAD
S01-FRA-00062-01	51	f	10/28/99	MD	QT + Torsade	20 mg qd	unk	Life threatening	Alcoholic
S01-DEN-01616-01	44	f	5/12/01	MD	Torsade	20 mg qd	60 days	hospitalization	no
S01-USA-00268-01	42	f	8/7/00	MD	VT QT +	40 mg 550 mg ??	unk	Life-threatening hospitalization	Cardiac arrhythmia Hepatitis c Drug abuse
S00-UKI-01202-01	76	f	unk	MD	QT + VT	20 mg qd	90 days	hospitalization	CHF
S00-USA-01487-01	unk elderly	f	unk	MD	VT VF	20 mg qd	unk	hospitalization	CAD Implantable defibrillator
S01-USA-02093-01	62	f	8/2/01	MD	QT + Syncope	20 mg qd	21 days	unk	COPD
S01-FIN-01644-01	23	m	6/30/01	MD?	Seizure (3min) QT +	40mg 20 mg	7 days	Hospitalization	Anorexia nervosa 1995
S01-SWE-0052701	47	f	2/26/01	MD	QT+ Syncope	20 mg qd	Unk to 2/26/01	hospitalization	no
S01-USA-00543-01	unk	unk	unk	MD	QT +	unk	unk	unk	unk
S02-USA-01458-01	unk	unk	unk	MD	QT +	unk	unk	unk	unk
S00GER-01018-01	unk	m	6/19/00	MD?	QT +	40 mg qd	unk	hospitalization	RBBB & on meds

Unk: unknown f:female m: male MD: medical doctor QT +: QT or QTc prolongation VT: ventricular tachycardia VA: ventricular arrhythmia

Table 2 Reported Cases not included in the sponsor's submission, MedWatch Database,

July 1998 through April 30,2002

Case Code	Age	Sex	Date of Event	Reporter	Diagnosis	Dosage	Duration	Outcome	History
A029665	23	f	6/15/00	PA	QT +	50 mg	90 days	Required intervention to prevent permanent impairment or damage	unk
2001UW-04122	unk	f	4/?/01	MD	VT QT+	unk	unk	hospitalization	QT+
A029665	23	f	6/15/00	PA	QT + PSVT	50 mg	90 days		unk
S02-UKI-00235-01	unk	f	12/8/01	MD	Seizure QT+	2240 mg once	once	hospitalization	none
S02-USA-00185-01	51	f	?/?/01	MD	QT + syncope	40	unk	hospitalization	QT+
S02-USA-00153-01	70	f	12/27/01	MD	QT +	40mgqd 60mgqd	3 years 3 days	hospitalization	Suicide ideation

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ON ORIGINAL

Table 3 Reported Cases, Post-Marketing review, *An updated Survey of QT Prolongation and Torsade de Pointes Arrhythmia, Citalopram in Therapeutic Doses and Overdose. H. Lundbeck Report., Up to June 30,2000*

Citalopram therapeutic dose- torsades de pointes/ ventricular arrhythmia

Case Code	Age	Sex	Date of Event	Reporter	Diagnosis	Dosage	Duration	Outcome	History
DKLU0991409(0)	unk	f	unk	unk	TdP	unk	unk	hospitalization	none
DKLU0950329(0)	85	f	8/30/95	MD	TdP	40 mg	48 days	death	AF
DKLU0960542(0)	84	f	7/11/86	unk	TdP	40 mg qd	95 days	death	DM, AF
DKLU0906949(0)	69	f	unk	unk	TdP Syncope	20 mg	Unk	hospitalization	DM
DKLU0990565(0)	84	f	2/5/99	authority	TdP AF	10 mg qd	25 days	hospitalization	CHF
DKLU0991754(0)	85	f	9/19/99	unk	QT + TdP	20 mg qd	115 days	hospitalization	DM
DKLU0950405(0)	62	m	10/5/95	unk	TdP QT +	20 mg	24 days	death	DM, RA
DKLU0960640(0)	25	f	8/23/94	unk	Syncope TdP	60 mg	93 days	hospitalization	Anorexia
DKLU0981158(0)	80	f	7/19/98	hospital	TdP	20 mg qd	49 days	hospitalization	HTN, AF
DKLU0990862(0)	65	m	4/9/99	unk	VT syncope	20 mg qd	unk	Life threaten	PVD CAD
DKLU0961160(0)	52	f	9/20/96	unk	QT + VF	20 mg qd	Unk	hospitalization	Kidney disease
DKLU0981678(0)	36	f	11/23/98	authority	QT + VF	10 mg qd	8 days	other	immunosuppression
DKLU0980606(0)	52	f	2/15/98	authority	polymorphic VT Syncope	20 mg qd	267 days	hospitalization	Syncope 1981
DKLU0991542(0)	89	F	7/24/99	Authority	VT convulsion	20 mg qd	unk	hospitalization	asthma

Citalopram therapeutic dose- QT prolongation

Case Code	Age	Sex	Date of Event	Reporter	Diagnosis	Dosage	Duration	Outcome	History
DKLU0970404(0)	77	f	unk	unk	QT + presyncope	40 mg qd	34 days	hospitalization	HTN
DKLU0996387(0)	56	F	7/1/99	Unk	QT + Syncope	30 mg qd	123 days	hospitalization	none
DKLU0200177	69	f	12/23/99	unk	Syncope QT +	40 mg	unk	hospitalization	none
DKLU0991089(0)	79	f	unk	unk	QT + Unstable angina	20mg qd	14 days	hospitalization	CAD
DKLU0991651(0)	85	f	10/29/98	unk	QT + Unstable angina	10 mg qd	5 days	hospitalization	CAD HTN
DKLU0990710(0)	47	f	Unk	unk	QT + bradycardia	40 mg qd	unk	hospitalization	Etoh abuse
DKLU0991162(0)	62	f	6/9/99	unk	QT +	50mg qd	41 days	other	MI
DKLU0980361(0)	unk	f	11/20/97	unk	QT +	40 mg	51 days	hospitalization	HTN, DM
DKLU0991392(0)	34	m	3/26/99	unk	QT +	30 mg qd	93 days	Unk	acne
DKLU1000737(0)	40	f	3/30/00	unk	QT +	10 mg qd	2 days	hospitalization	depression
DKLU0991813(0)	38	unk	unk	unk	QT +	20 mg qd	unk	unk	none
DKLU0980366(0)	unk	m	12/9/97	unk	QT +	20 mg qd	26 days	hospitalization	none
DKLU0980367(0)	unk	m	12/16/97	unk	QT +	40 mg qd	unk	hospitalization	none
DKLU0980368(0)	unk	f	12/9/97	unk	QT +	20 mg qd	unk	hospitalization	none
DKLU0980490(0)	unk	f	1/7/98	unk	QT +	20 mg qd	unk	unk	none
DKLU0980727(0)	unk	f	unk	unk	QT +	40 mg qd	unk	unk	none
DKLU0990171(0)	58	m	6/28/98	unk	QT +	40 mg qd	150 days	unk	none
DKLU0990445(0)	29	m	7/28/98	Hospital	QT +	20mg qd	14 days	hospitalization	none
DKLU0991151(0)	64	F	6/17/99	Authority	QT +	Unk	Unk	hospitalization	Psych disorder
DKLU0991978(0)	Unk	f	unk	unk	QT +	20 mg qd	unk	other	none
DKLU1000001(0)	48	M	3/15/00	unk	QT +	40 mg	unk	hospitalization	none

Citalopram- Overdose

Case Code	Age	Sex	Date of Event	Reporter	Diagnosis	Dosage	Duration	Outcome	History
DKLU0200028(2)	35	m	11/30/99	unk	QT +	overdose CIT only	once	hospitalization	None
DKLU1000032(0)	60	m	10/8/99	authority	QT +	overdose CIT only	once	other	HTN
DKLU0960100(0)	45	f	2/6/96	unk	QT +	Overdose CIT only	unk	hospitalization	depression
DKLU1000051(0)	14	f	4/10/00	unk	QT +	Overdose CIT only	once	hospitalization	Psych disorder
DKLU0970890(0)	45	f	unk	National Poison center	QT +	Overdose CIT only	unk	hospitalization	none
DKLU0970526(0)	26	f	1/17/97	unk	QT + convulsion	Overdose CIT only	unk	hospitalization	none
DKLU0990881(0)	16	f	unk	unk	QT + convulsions	Overdose CIT only	1 time	hospitalization	none
DKLU0991467(2)	35	m	8/13/99	unk	QT + convulsion	Overdose CIT only	1 day	hospitalization	Drug abuse
DKLU0991700(0)	18	F	9/21/98	unk	QT + convulsion	Overdose CIT only	1 day	hospitalization	suicidal
DKLU0960175(0)	22	f	unk	unk	QT + Convulsion	Overdose CIT only	unk	hospitalization	unk
DKLU1000039(1)	19	m	4/13/00	unk	QT + seizure	Overdose CIT only	once	hospitalization	Drug abuse
DKLU0970893(0)	22	f	unk	National poison center	QT + bradycardia hypotension	Overdose CIT only	unk	hospitalization	none
DKLU0200342(0)	21	f	12/9/99	unk	QT +	Overdose mixed	unk	unk	none
DKLU0970012(0)	27	f	9/20/96	unk	QT +	Overdose nixed	unk	hospitalization	Drug abuse
DKLU0970592(0)	25	f	4/16/97	Health Authority	QT +	Overdose mixed	1 day	hospitalization	none
DKLU0970527(0)	44	m	12/1/96	unk	QT +	Overdose mixed	1 day	hospitalization	Psych problem
DKLU0970525(0)	32	f	10/13/96	unk	QT + convulsions	Overdose mixed	1 day	hospitalization	none
DKLU0990151(0)	26	f	1/20/99	unk	QT + seizure	Overdose mixed	1 day	hospitalization	bulimia
DKLU0970528(0)	42	m	10/8/94	unk	QT + convulsions	Overdose mixed	1 day	hospitalization	depression
DKLU0991407(0)	23	f	8/1/99	unk	QT + convulsion	Overdose mixed	unk	unk	suicidal
DKLU0960180(0)	35	f	unk	unk	QT + convulsions	Overdose mixed	unk	hospitalization	unk
DKLU0970730(0)	47	m	8/10/97	unk	QT + Torsade	Overdose mixed	unk	hospitalization	Cancer
DKLU0200255(0)	40	f	unk	unk	Convulsions VT	Overdose mixed	unk	hospitalization	migraine

Appendix 2

DEPARTMENT OF HEALTH & HUMAN SERVICES
Public Health Service

Division of Scientific Investigations
Office of Medical Policy
Center for Drug Evaluation and Research
Food and Drug Administration
Rockville MD 20857

CLINICAL INSPECTION SUMMARY

DATE: June 19, 2002

TO: Paul David, R.Ph., Senior Regulatory Project Manager
Karen Brugge, M.D., Medical Officer
Division of Neuropharmacological Drug Products, HFD-120

THROUGH: Antoine El-Hage, Ph.D., Chief
Good Clinical Practice Branch II, HFD-47
Division of Scientific Investigations

FROM: Ni A. Khin, M.D., Medical Officer
Good Clinical Practice Branch II, HFD-47
Division of Scientific Investigations

SUBJECT: Evaluation of Clinical Inspections

NDA: NDA 21-440

APPLICANT: Forest Laboratories, Inc.

DRUG: Escitalopram Oxalate Tablets

THERAPEUTIC CLASSIFICATION: Type S, Standard Review

INDICATION: Major Depressive Disorder Relapse Prevention

CONSULTATION REQUEST DATE: January 14, 2002

ACTION GOAL DATE: June 29, 2002

I. BACKGROUND:

Escitalopram (Lu 26-054) is the S-enantiomer of the selective serotonin reuptake inhibitor citalopram, which is currently marketed under the brand name of Celexa for depression. In 2001, the sponsor has submitted the use of escitalopram in major depressive disorder under NDA 21-323. In this NDA 21-440, the sponsor has requested the use of escitalopram in relapse prevention of major depressive disorder.

Inspection assignments were issued on February 28, 2002 for two domestic sites, Drs. Doraiswamy and Heiser for Protocol SCT-MD-03. According to protocol SCT-MD-03, the subjects received flexible dose of escitalopram for 8 weeks (open label phase) followed by fixed dose (max: 20mg/day) or placebo-control for 36 weeks (double blind phase) for prevention of depression relapse. The inspection was for the purpose of validating data in support of pending NDA 21-440.

II. RESULTS (by site):

NAME	CITY	STATE	ASSIGNED DATE	RECEIVED DATE	CLASSIFICATION
Doraiswamy	Durham	NC	02-28-2002	05-20-2002	VAI*
Heiser	Newport Beach	CA	02-28-2002	06-17-2002	NAI

Doraiswamy, M.D.

At this site, 12 subjects who completed the lead-in study, SCT-MD-01, continued into protocol SCT-MD-03 with 4 subjects completing the study. The discontinuation reasons included lack of efficacy (3 subjects), protocol violation (1 subject) and personal reasons/withdrew consent (4 subjects).

An audit of 12 records was conducted. Signed and dated informed consents were present for all the participants.

Inspectional findings revealed identical EKG tracings for the following subjects in the lead-in-study, SCT-MD-01 and study 03.

It appeared that EKG memory clear button error was identified after the FDA investigator noticed identical tracings obtained for 2 to 3 consecutive subjects in five separate occasions. Specifically, EKG user manual given to the sites and the sponsor files specified that clear memory button be held for 5 seconds to erase prior EKG while it was needed for 30 seconds. Each pair or trio of identical tracings occurred in sequence, which suggested the device error.

According to the protocol (SCT-MD-03), EKG measurements were required at baseline visit 1(final visit of the lead-in study: SCT-MD-01), visit 5 (week 6 of the open-label phase) and visit 16 (week 44 of double-blind phase) or upon early termination when the patient discontinued prior to week 44. As per the study procedure, all baseline EKGs were processed by ( ) and the reports were sent to the study site for the investigator's evaluation. EKGs performed at other time points were reviewed at each center.

At this site, twelve subjects enrolled in the protocol SCT-MD-03 from the lead-in study SCT-MD-01. The EKG problem was identified in 11 subjects as per FDA-483. In Dr. Doraiswamy's written response dated April 18, 2002, it was stated that he has reviewed every EKG done in both SCT-MD-01 and SCT-MD-03. Among the 39 EKGs done, he discovered that there were 7 duplicate traces of 5 EKGs. Of these 7 duplicate tracings, 3 occurred at the screening visit of SCT-MD-01. Of these 3, one subject was a screen failure who never received the study drug, the second subject had normal EKG at other time points done with different machines and the third had no history of cardiac disease. All 4 patients with potential duplicate traces at end point of SCT-MD-01 had normal EKGs at entry and at least one also had normal EKGs at other time points using other machines. No subject identifiers were mentioned and no assurance that these EKGs are valid at this site.

Dr. Doraiswamy has taken appropriate steps by informing the sponsor and the IRB in regards to this matter. However, it appeared that he did not evaluate the subjects' EKGs thoroughly as he did not recognize these identical tracings until it was pointed by the FDA investigator. This would have had an effect on subjects' safety.

In his response to FDA-483 inspectional findings, it was also noted that "the sponsor verbally informed me that they are examining all EKG done using this device in this study and that their initial review showed that one or more duplicates were also found at other sites." If this issue is of concern, I suggest that the Review Division should check with the sponsor, to examine their safety database for similar problem at other sites and report to the FDA.

Overall, the efficacy data appear acceptable. DSI recommends excluding the EKG safety data generated at this site.

Heiser, M.D.

There were 17 subjects entered into the study; 12 of which were randomized and 7 subjects completed the study. An audit of 17 records was conducted. No significant deviation from regulation was noted. Signed and dated informed consents were present for participants.
Data appear acceptable.

III. OVERALL ASSESSMENT OF FINDINGS AND GENERAL RECOMMENDATIONS

Overall, the efficacy data from these two domestic sites appear acceptable for use in support of the pending NDA.

As stated above, DSI recommends the Review Division to consider excluding the EKG safety data generated at Dr. Doraiswamy's site and checking with sponsor if the safety database contains similar problems with EKGs done at other sites.

Recently, DSI has investigated eResearch to find the extent of this problem in relation to other studies. The Review Division will be informed accordingly as additional information is obtained.

There was no limitation to these inspections.

[Note: The review and evaluation of the Heiser audit was based on the FDA Investigator's Preliminary Summary of Findings. Should the EIR and exhibits from the audit, when received, contain additional information that would significantly effect the classification or have an impact on the acceptability of the data, we will inform the review division accordingly.]

Key to Classifications
NAI = No deviation from regulations. Data acceptable
VAI = Minor deviations(s) from regulations. Data acceptable
VAIr= Deviation(s) form regulations, response requested. Data acceptable
OAI = Significant deviations for regulations. Data unreliable
Pending = Inspection not completed

Ni A. Khin, M.D., Medical Officer
Good Clinical Practice Branch II, HFD-47
Division of Scientific Investigations

cc:
NDA 21-440
Division File
HFD-45/Program Management Staff (electronic copy)
HFD-47/c/r/s
HFD-47/Khin
HFD-47/Friend
HFD-45/RF

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This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

David Gan
7/12/02 10:18:55 AM
MEDICAL OFFICER

Judith Racoosin
7/12/02 03:40:40 PM
MEDICAL OFFICER

APPEARS THIS WAY
ON ORIGINAL

Review of Clinical Data

NDA:	21-323
Drug Name:	Generic Name: Escitalopram Trade Name: Lexapro
Sponsor:	Forest labs
Material Reviewed:	Pregnancy labeling
Reviewer:	Gerard Boehm, MD, MPH
Date Completed:	7/24/02

Background

In a 2/02 submission, the sponsor proposed the following statement for the pregnancy section for escitalopram labeling:

[redacted]

The sponsor referenced the following publication: Ericson A, Kallen B, Wiholm BE; Delivery Outcome after the use of antidepressants in early pregnancy, Eur J Clin Pharmacol (1999) 55:503-508, as justification for their proposed labeling statement.

Methods

The referenced publication describes results from an analysis of Swedish Medical Birth Registry data for the years 1995-1997. This registry contains information about all births in Sweden and includes medical documents from antenatal clinic, at delivery, and from pediatric examinations of the newborn. The registry recorded medication use that pregnant women reported at their first visit to the antenatal clinic (usually week 10-12, with 92% before the end of week 16). This information sometimes but not always included dosage and timing of medication use. Outcome information came from the Medical Birth Registry as well as the Registry of Congenital Malformations. In this study, the outcome variables were multiple births, short gestational duration (<32 weeks, <37 weeks), low birth weight (<1500g, <2500g) in singletons, perinatal mortality and presence of congenital malformations. The investigators compared the number of outcomes among *any antidepressant* users, *only SSRI* users and *only non-SSRI* users to the number expected. The expected number of events was derived from the registry data for all births and was stratified by maternal age, parity, and smoking habits during pregnancy. The investigators did not compare the number of observed vs. expected outcomes for the citalopram-exposed group.

Results

The investigators identified 531 mothers exposed to one or more SSRI antidepressants with the following breakdown: citalopram n=364; paroxetine n=118; sertraline n=32; fluoxetine n=15; citalopram+sertraline n=1; paroxetine+sertraline n=1. Fifteen mothers reported use of an SSRI and a non-SSRI, and 431 mothers reported use of one or more non-SSRI antidepressants.

The investigators identified a total of 376 mothers who reported citalopram use. Three hundred sixty-four mothers reported citalopram use without reporting use of another antidepressant and one mother reported use of citalopram plus sertraline. Eleven

mothers reported citalopram use with another non-SSRI antidepressant (7 clomipramine, 2 amitryptiline, 2 imipramine).

The investigators reported fewer twin births than expected in the *any antidepressant* group (11 observed, 15.9 expected, RR=0.69, 95% CI 0.35-1.24) and in the *only SSRI* group (2 observed, 8.5 expected, RR=0.24 95% CI 0.03-0.85). They reported that infant survival and presence of congenital malformations did not significantly deviate from the expected numbers (*any antidepressant* observed deaths 7, expected 5.8; malformed infants observed 39, expected 34.4; *only SSRI* observed deaths 4, expected 2.6, malformed infants observed 21, expected 18.7).

Fifteen infants with mothers reporting citalopram use had congenital malformations. In this group there were 4 infants with an undescended testicle and one infant with each of the following malformations: pre-auricular appendix, hypoplastic left heart syndrome with hypospadius, patent ductus arteriosus, unspecified cardiac defect, cleft lip and palate, duodenal atresia, hypospadius, hydronephrosis, unstable hip, trisomy 13, and laryngeal/bronchial anomaly.

The sponsor stated that there was no difference in anomaly rate among citalopram and the other SSRI-exposed infants (p=0.72). The investigators provided no such comparison for twin births, infant survival, short gestational duration, or low birth weight.

Discussion

The sponsor referenced a published study to support escitalopram pregnancy labeling information. A strength of the referenced study was the identification of the exposure prior to knowing the outcome of the pregnancy, eliminating the potential reporting bias associated with voluntary pregnancy registry data. The investigators identified two weaknesses of the study, the lack of information about dose and timing of exposure, and potential underreporting of antidepressant use by pregnant females. Additionally, the study is not sufficiently powered to detect potentially important increases in risk for specific malformations.

I do not believe that the sponsor's pregnancy labeling clearly reflects the findings presented in their reference study because the wording appears to suggest that the study included specific risk comparisons for the citalopram group. The sponsor would state in labeling, that in the cited study, citalopram did not affect the incidence of low birth weight, perinatal mortality or congenital malformations. Without reading the referenced study, one would assume that the statement is based on risk comparisons for those mothers taking citalopram and those not taking this medication. The referenced study made no such comparisons. The only comparison that the investigators made for the citalopram group was to other SSRI exposed infants (no difference in anomaly rate). Even though the majority of exposures in the overall SSRI group were to citalopram (68%, 365/531), we do not know if the pregnancy outcome profile for citalopram is identical to the overall SSRI group.

Even if the appropriate risk comparisons were available, one must acknowledge that we have no information about whether the risks for adverse pregnancy outcomes for citalopram provide insight about the risks with escitalopram.

Recommendations

I recommend striking the following sentence in proposed escitalopram labeling:

The sponsor should approach the study investigators and request the data needed to make adverse pregnancy outcome risk comparisons for the citalopram group. This information could be useful in the citalopram labeling and one could consider the relevance of including such information in the escitalopram labeling.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Jerry Boehm
7/24/02 06:38:44 AM
MEDICAL OFFICER

Judith Racoosin
7/24/02 12:58:28 PM
MEDICAL OFFICER

APPEARS THIS WAY
ON ORIGINAL

Review and Evaluation of Clinical Data

Safety Team Leader Review of Response to Approvable Letter

NDA: 21-323
Drug: escitalopram
Route: oral
Indication: major depressive disorder
Sponsor: Forest Laboratories
Action Date: 8-19-02
Date Review Completed:

1 Background

During the review of the escitalopram NDA, primary medical reviewer Dr. Karen Brugge noted that clinical pharmacology study 98107 showed evidence of QTc prolongation at the highest escitalopram (SCIT) and citalopram (CIT) levels.

		QTc Mean change from baseline to last study dose
Escitalopram	10 mg	-1 msec
	30 mg	11 msec
Citalopram	20 mg	4 msec
	60 mg	10 msec

Given these findings, the DNDP safety team was asked to review the pertinent ECG data. A request was sent to the sponsor asking for details regarding the conduct of the ECG monitoring in the various parts of the SCIT development program, reanalysis of the SCIT QT findings using the Fridericia correction, and a summary of the postmarketing experience with citalopram as it pertained to QT/QTc prolongation, torsades de pointes, and ventricular arrhythmia.

Dr. David Gan of the DNDP safety team reviewed the sponsor's response to the Division's information request. During the course of the review of Forest's response, the Division was notified by CDER's Division of Scientific Investigation that an audit of one of the study sites had identified a number of duplicate ECGs observed for multiple patients. Dr. Gan's review describes the sponsor's investigation of the duplicate ECG problem. Ultimately, the sponsor was required to reanalyze the pooled ECG data from the pivotal trials because 13 placebo, 25 SCIT, and 16 CIT patients had to be excluded for duplicate ECGs. The sponsor was not able to access these patients' original tracings, as the ECG machines had not been appropriately cleared prior to their recording.

A large part of the sponsor's submission reviewed the postmarketing experience of citalopram (the racemate of escitalopram) with regard to QTc prolongation, and associated ventricular arrhythmias. My supervisory review will briefly review the clinical trial findings and then focus on the postmarketing experience.

2 Clinical Trial Findings

2.1 *Clinical Events Potentially Related to QTc prolongation*

In Dr. Brugge's review of the original SCT NDA submission, she did not identify any deaths, SAEs, or discontinuations due to AEs that were attributed to ventricular arrhythmia or TdP in ten clinical pharmacology studies or four large phase III trials in major depressive disorder. No subject had a QTc interval duration that exceeded 500 msec. Among patients who had a normal baseline ECG and an abnormal endpoint ECG, a proportion had the reason for the abnormal ECG as "QTcB dispersion increased" or "QTcB dispersion prolonged". The sponsor stated that the two terms were used interchangeably, and that the definition was QTcB dispersion greater than >100 msec or >100% increase in dispersion. The proportion of patients with this finding was 14.5%, 11.5%, and 16.7% for the placebo, SCT, and CIT groups, respectively.

Study MD-03 was a double-blind placebo-controlled relapse prevention trial conducted in patients with major depressive disorder who responded to eight weeks of open label treatment with SCT. No patients died, and no serious adverse events or discontinuations due to adverse events described QT prolongation, ventricular arrhythmia, or TdP. One patient had a QTc length that exceeded 500 msec; the outlier value of 517 msec (increase from baseline 414 msec) was identified during open label SCT treatment and persisted during treatment with the study drug.

In the safety update submitted with the response to the approvable letter, no patients died, and no serious adverse events described QT prolongation, ventricular arrhythmia, or TdP.

2.2 *Clinical Pharmacology Study 98107*

As part of the safety team examination of the clinical pharmacology ECG data, I requested that the sponsor submit the QTc data from 98107 using Fridericia's correction (submitted by email 7/11/02). The results are shown in the table below.

Study 98107- mean QTc (Fridericia correction) values by dose group and study day

	Screening	Baseline (day before first dose)	Day 2 (day after first dose)	Day 24 (last dose day)	Day 34
CIT 20 (n=18)	.371	.366	.376	.376	.366
CIT 60 (n=18)	.371	.372	.375	.387	.380
SCIT 10 (n=17)	.370	.366	.377	.371	.372
SCIT 30 (n=17)	.371	.367	.382	.386	.377

Using the values in the above table, I calculated the mean change from baseline by dose group and study day.

Study 98107 QTc mean change from baseline

	Day 2-Baseline	Day 24- Baseline
CIT 20 (n=18)	10	10
CIT 60 (n=18)	3	15
SCIT 10 (n=17)	11	5
SCIT 30 (n=17)	15	19

These mean change values do not match those from the summary data above derived from Dr. Brugge's primary review. The difference is likely related to the method of QT correction for heart rate used, but we will verify this with the sponsor. Although the data is hard to interpret in the absence of a placebo group, there still appears to be evidence of an ability for escitalopram to prolong the QTc interval.

2.3 *Sponsor's reanalysis of phase III trials ECG data following exclusion of duplicate ECGs and including Fridericia's correction*

Table 2 ***Mean Changes in ECG Parameters Safety Update***

ECG Parameter	*Placebo (N=592)*		*Escitalopram (N=715)*		*Citalopram (N=408)*	
Heart Rate	540	0.3	650	-2.3	367	-2.4
	527	**0.3**	**625**	**-2.2**	**351**	**-2.7**
QT Interval	540	-0.2	650	7.5	367	7.6
	527	**-0.0**	**625**	**7.4**	**351**	**8.2**
QTcB Interval (Bazett)	540	0.8	650	2.0	367	1.6
	527	**0.9**	**625**	**1.9**	**351**	**1.2**
Adjusted QTcB Interval (Bazett)	540	1.1	650	1.8	367	1.7
	527	**1.5**	**625**	**1.9**	**351**	**1.5**
QTcF Interval (Fridericia)	540	0.4	650	4.0	367	3.7
	527	**0.5**	**625**	**3.9**	**351**	**3.7**
Adjusted QTcF Interval (Fridericia)	540	0.6	650	4.0	367	3.7
	527	**0.9**	**625**	**4.1**	**351**	**3.7**

Revisions are indicated in **bold**.
Adjusted QTc intervals are the least squares means obtained from the ANCOVA model with treatment and study as factors and baseline value as covariate.
Data drawn from SCT-MD-01, SCT-MD-02, 99001, and 99003

Based on the cohort of patients with unduplicated ECGs, using the Fridericia QT interval heart rate correction, the clinical trial data showed a prolongation of 4.1 for SCIT and 3.7 for CIT, compared with 0.9 for placebo. It must be kept in mind that the change from baseline analyses for the four large clinical trials were based on a single baseline ECG and a single end of study ECG, conducted without regard to the timing of the last dose of study drug.

3 Postmarketing experience

Citalopram, the racemate of escitalopram, has been marketed in Europe since 1989 and in the US since July 1998. The sponsor submitted the following components to describe their postmarketing experience with citalopram:

- "Post-Marketing Review of QT/QTc Prolongation, Torsades de Pointes, Ventricular Tachycardia, Ventricular Arrhythmia, and Citalopram Therapy"
  - covers the period from 7/1/2000 through 11/30/2001
  - updates Lundbeck (licensing partner) report 72/345 "An Updated Survey of QT Prolongation and Torsade de Pointes Arrhythmia. Citalopram in Therapeutic Doses and Overdose" encompassing the period "up through 6/30/2000"[1] and dated 12/22/2000.

For simplicity, I will refer to the Forest report and the Lundbeck report. All postmarketing cases are summarized in Appendix I in tables reproduced from Dr. Gan's review (with some modifications- see Appendix I below).

3.1.1 The Forest Report

During the period 7/1/2000 through 11/30/2001, Forest identified 15 serious adverse events and three domestic non-serious events using the following search terms: *ventricular tachycardia, ventricular arrhythmia, ventricular fibrillation, torsades de pointes, or QT/QTc prolongation.* Although six foreign non-serious reports were identified by the search (5 QT/QTc prolongation and 1 ventricular arrhythmia), Forest did not have access to these reports.

Table 1 of Dr. Gan's review summarizes the 18 reports identified. The sponsor asserts that causality assessment with citalopram is hindered in 16 of the 18 cases due to limited information (n=5) or confounding factors (n=11). They conclude that two cases "merit consideration" as being related to citalopram therapy. One of these cases (**S00-UKI-01907-**

[1] The report does not include a start date for the time period covered by the report; further clarification from the sponsor suggests that the report is inclusive of all cases of QTc prolongation reported from the time of the original clinical trials in 1985.

01) describes a 58 year old woman who developed ventricular tachycardia a few hours after a single 20 mg dose of citalopram. The patient was hospitalized, treated with verapamil, and recovered. Her history was significant for hypertension, "cardiovascular disorder", and cerebrovascular disease status post carotid endarterectomy. The second case[2] (LO1-USA-01339-01) believed to "merit consideration" by the sponsor was an overdose case in which a 21 year old woman prescribed 30 mg of citalopram daily took an intentional overdose of 400 mg of citalopram along with alcohol and one tablet of alprazolam. Over the course of the next 24 hours the patient's QTc interval went from 385 msec at admission to a peak of 457 msec at 13 hours, and back to 353 msec at 21 hours post overdose.

One other report (S01-USA-01623-01) described a suicide attempt in which a male patient ingested 200 tablets of citalopram (unknown dosage strength) along with 50-90 clonazepam tablets. The patient was hypotensive on admission and later was found to have evidence of a non-Q wave myocardial infarction and QT prolongation on ECG. Citalopram was discontinued; cardiac catheterization and a follow-up ECG were "normal".

Two of the cases identified by the sponsor had the outcome of death. One case (S00-USA-01913-01) is impossible to interpret because the report comes from a Forest sales representative who heard that a physician speaking for another pharmaceutical company told other physicians that in his practice, citalopram caused QT prolongation and death. However, there was no information provided to identify an actual patient. The second death (S01-USA-00206-01) occurred in a 42 yo female with a history of asthma and heavy smoking who had been taking citalopram for an unspecified period of time. While shopping the patient complained of intermittent chest pain and feeling faint. Later, while driving in a car, the patient died suddenly. The county medical examiner classified the cause of death as unknown, although he speculated that it was due to ventricular arrhythmia.

Five of the cases identified by the sponsor described torsade de pointes (TdP). Four of the cases were confounded for different reasons, including history of QT prolongation prior to initiation of citalopram therapy (S01-NOR-00229-01), history of coronary heart disease in an elderly patient (S01-GER-01168-01), history of cardiac arrhythmia (not otherwise specified) with hypomagnesemia at the time of the event (S01-USA-00268-01), and hypokalemia (S01-FRA-00062-01). A fifth case (S01-DEN-01616-01) described a 44 yo woman with no reported medical history who after taking citalopram for about two months was hospitalized when she experienced TdP. The outcome was unknown, except that the patient stopped citalopram nine days later. Mirtazepine was also listed as a suspect drug, but according to the report, it wasn't initiated until four days after the patient was hospitalized for TdP.

Two other cases identified by the sponsor described ventricular tachycardia. Each of these cases was confounded by concurrent cardiac conditions including hypokalemia and

[2] Published as QTc Interval Prolongation Associated with Citalopram Overdose: A case report and literature review. *Clinical Neuropharmacology* 2001; 24(3): 158-62.

post-surgical state in a 76 yo female with congestive heart disease (S00-UKI-01202-01) and coronary artery disease in an elderly female with an implantable defibrillator (S00-USA-01487-01).

Three other cases reported by the sponsor described syncope or seizure in association with QT prolongation. One case (S01-USA-02093-01) described a 62 yo female with history of COPD who experienced two episodes of syncope within the first three weeks on citalopram. Her ECG showed a QTc of 510 msec which was prolonged compared to a previous ECG done before citalopram therapy (QTc 480 msec). Following discontinuation of citalopram, the patient had a normal cardiac work-up including Holter monitor and signal-averaged ECG. The second case (S01-FIN-01644-01) described a 23 yo male who was titrated up from 20 mg of citalopram and 20 mg of buspirone to 40 mg of both drugs after five days on the lower dose. On the first day of the higher dose, the patient experienced a grand mal seizure. Subsequent work-up in the hospital revealed QT prolongation on the ECG, normal blood chemistry, and a normal head CT. The patient was titrated back down to 20 mg of each of the drugs. There was no additional information regarding follow-up ECG. According to the report, the patient had been treated with the two drugs for anorexia nervosa two years previously without difficulty. In the third case (S01-SWE-0052701), the patient was hospitalized for syncope after about one year on citalopram therapy. She was found to have QT prolongation on ECG and hypokalemia. Citalopram was discontinued and about two weeks later she was hospitalized for another syncopal episode.

The final three cases described QT prolongation alone. Two of these reports (S01-USA-00543-01, S02-USA-01458-01) were characterized by limited information, and the third report described what appeared to be minimal prolongation (S00GER-01018-01).

3.1.2 MedWatch Reports

In Table 2 of Dr. Gan's review, he summarizes five cases of QT prolongation reported in association with citalopram to MedWatch that were not submitted as part of the sponsor's submission. One case (A029665) of paroxysmal supraventricular tachycardia with associated QTc prolongation occurred 35 days after the patient had discontinued citalopram. Another case (2001UW04122) described ventricular tachycardia and QT prolongation in a woman in her sixties who had a history of "slight QT prolongation". Esomeprazole, which was started more proximal (a few weeks) to the event, was also a "suspect" drug. A case (S02USA0018501) of syncope and QT prolongation was reported by a patient (who was a physician). She reported that she fainted while taking citalopram 40 mg daily; her QTc was 580 mg. She decreased the dosage to 20 mg and has not had recurrence of syncope, although the QTc interval had not been remeasured. A positive dechallenge case (S02USA0015301) of QT prolongation was reported in a patient hospitalized for suicidal ideation. On admission her citalopram dose was increased from 40 mg to 60 mg daily. Her follow-up ECG showed QT prolongation compared to the baseline. The dose was decreased back down to 40 mg and a subsequent ECG showed normalization of the QT interval. The heart rate-corrected QT intervals were not reported. The fifth case (S02UKI0023501) described an overdose case of citalopram (2240 mg) along

with an unknown amount of ethanol. The patient experienced a grand mal seizure; an ECG showed left bundle branch block and prolonged QT. The outcome was unknown as the patient was transferred to another hospital.

3.1.3 The Lundbeck Report

During the period from the clinical development of citalopram up through 6/30/2000, Lundbeck identified 14 cases of TdP or ventricular arrhythmia, 21 cases of QTc prolongation, and 23 cases of citalopram overdose with report of TdP, ventricular arrhythmia, or QTc prolongation using the following search terms: *ventricular tachycardia, ventricular arrhythmia, ventricular fibrillation, torsades de pointes, or QT/QTc prolongation.* These reports are summarized in Table 3 of Dr. Gan's review.

3.1.3.1 Therapeutic dose cases

3.1.3.1.1 Torsades de pointes/ventricular arrhythmia cases

Fourteen reports described TdP (n=9) or another ventricular arrhythmia (n=5). The interpretation of one TdP case **(DKLU0991409)** was hindered by limited information. The other eight TdP cases were confounded for a variety of reasons including cardiovascular comorbidities (n=5; **DKLU0950329, DKLU0960542, DKLU0906949, DKLU0990565, DKLU0991754**), concurrent hypokalemia (n=2; **DKLU0950405, DKLU0960640**), and concomitant use of a known torsadogenic drug **(DKLU0981158)**. Of the five reports of ventricular arrhythmia, two were confounded by cardiovascular comordities **(DKLU0990862, DKLU0961160)**; and one **(DKLU0981678)** was confounded by low serum magnesium and concomitant use of a QT prolonger. An additional case **(DKLU0980606)** describing polymorphic VT in a 52 yo female was suggestive of a relationship to citalopram; however, the patient had persistent syncope 17-18 days after citalopram was discontinued. Finally, an 89 yo female **(DKLU0991542)** with a history of hypertension, valvular disorder, and dementia experienced loss of consciousness followed by seizure and "short ventricular tachycardia attacks". She was recovered following treatment in the ICU and discontinuation of citalopram. Serum levels of citalopram and its metabolite drawn 27 hours after the patient's presentation showed high levels, suggesting an overdose. This was not confirmed, however.

3.1.3.1.2 QTc prolongation cases

Twenty-one reports described QT or QTc prolongation in association with citalopram therapy. Of the three cases in which syncope or presyncope was reported along with QT or QTc prolongation, two had negative dechallenge **(DKLU0970404)**, with one of the two having a negative rechallenge **(DKLU0996387)**. In the third case **(DKLU0200177)**, QT prolongation was identified as having been noted prior to initiation of citalopram therapy. Two reports of QT prolongation were associated with presentations of unstable angina. In one of these cases **(DKLU0991089)**, the QT interval was prolonged (600 msec), but the heart rate corrected QTc value was within normal limits (420 msec). In the other case **(DKLU0991651)**, the QT prolongation was documented on the day prior to the onset of

unstable angina; it is hard to evaluate the source of the QT prolongation given the active CAD. In one other case (**DKLU0990710**), QTc prolongation was reported to have been present while the patient was on 20 mg daily of citalopram (453 msec), but worsened slightly after an increase to 40 mg daily (463 msec); this worsening was also temporally associated with asymptomatic but severe bradycardia (HR=34). Following discontinuation of citalopram, the QTc decreased to 440 msec.

In three cases (**DKLU0991162, DKLU0980361, DKLU0991392**) QT or QTc prolongation was noted while the patient was on citalopram and then reported to resolve after discontinuation or decrease of the dose. The first patient mentioned above was known to have substantial CAD and CHF. A fourth case of QT prolongation (**DKLU1000737**) also showed this pattern, but the data presented suggests that the patient may have had concomitant hypokalemia.

One case provided limited information for interpreting the report of QT prolongation (**DKLU0991813**). Seven of the reports of QT prolongation (**DKLU0980366, DKLU0980367, DKLU0980368, DKLU0980490, DKLU0980727, DKLU0990171, DKLU0990445**) were confounded by the concomitant use of sertindole, a known QT prolonger. Three other cases were confounded by use of other medications that may have been responsible for the QT prolongation (**DKLU0991151**- IM haloperidol; **DKLU0991978**-clarithromycin; **DKLU1000001**-desipramine [prolonged QTc resolved during continuation of CIT]).

3.1.3.2 Overdose cases

Twenty-three of the 58 reports described in the Lundbeck report described overdose cases. Twelve of the 23 overdose cases reported citalopram as the only ingested substance. For these twelve cases, the median amount ingested was 800 mg (range 100-3600), and the mean amount ingested was 1055 mg. These mean and median were not substantially different from those values for the entire cohort of overdose cases. Among the "citalopram only" overdoses, five (**DKLU0200028, DKLU1000032, DKLU0960100, DKLU1000051, DKLU0970890**) described QT or QTc prolongation alone[3], six (**DKLU0970526, DKLU0990881, DKLU0991467, DKLU0991700, DKLU0960175, DKLU1000039**) described QT or QTc prolongation and convulsions or probable seizure, and one described QT prolongation and severe bradycardia and hypotension. This last patient (**DKLU0970893**) was a 22 yo female who ingested fifty 20 mg citalopram tablets and presented to the hospital sedated and with nystagmus. Her pulse fell from 64 to 30 bpm and her blood pressure fell from 130/80 to 70 systolic. "Prolonged QT interval improved rapidly." There was a "remaining tendency" to bradycardia at rest. The QT interval normalized.

Among the 11 other overdose cases that involved other drugs in addition to citalopram, four (**DKLU0200342, DKLU0970012, DKLU0970592, DKLU0970527**) described QT or QTc prolongation alone, five (**DKLU0970525, DKLU990151, DKLU0970528, DKLU991407, DKLU0960180**) described QT or QTc prolongation and convulsions or probable seizure, one described QTc prolongation and TdP, and one described ventricular tachycardia and

[3] One patient (DKLU01000032) was taking concomitant thioridazine, a known QT prolonger.

convulsions. The TdP case (**DKLU0970730**) described a 47 yo male with a history of alcohol abuse, "investigation for ischemic heart disease", "operation for abdominal cancer", and pre-existing T wave abnormalities who attempted suicide by ingesting 2000 mg of citalopram, 400 mg of temazepam, and an unspecified amount of ethanol. He was hospitalized with a prolonged QT interval and attacks of TdP. The first night he had a brief seizure coincident with an episode of ventricular fibrillation. Over the next 24 hours the patient had additional runs of ventricular tachycardia, and at least one other episode of ventricular fibrillation requiring cardioversion. The first documented QTc interval was 456 msec, with a peak 20 hours later at 502 msec; three days later the QTc was 426 msec, but one week after admission it was prolonged again at 470 msec. The patient's potassium was noted to be borderline low on the second day of admission (3.5 mmol/L), but the value at the time of admission was not reported. No additional information was provided. The ventricular tachycardia case (**DKLU0200255**) reported a 40 yo female who took 280 mg of citalopram and 600 mg of tranylcypromine. She presented to the hospital with convulsions and ventricular tachycardia. QT prolongation was **not** reported. The patient made a "complete recovery".

4 Discussion

During the preclinical studies of citalopram (racemate), there was a signal for sudden death in a chronic toxicology study in dogs; the deaths were attributed to the QTc prolonging effects of a citalopram metabolite, didemethylcitalopram (DDCT). These findings are described in the "Animal Toxicology" section at the end of the citalopram labeling. DDCT was found to be present only in small amounts in humans, so it was not believed at the time of citalopram approval to be a risk for clinical use of the drug.

Results of a multiple dose crossover clinical pharmacology study (98107) suggested that at the high end of the dosing regimen, both citalopram and SCT were associated with a modest prolongation of the QTc (10-11 msec). Examination of the QTc data from 98107 using Fridericia's correction (more appropriate than Bazett's, since escitalopram has a mild bradycardic effect) showed evidence of a more marked QTc prolongation (15-19 msec at the 30 mg SCIT dose). Reanalysis of the ECG data from clinical trials (following the purging of duplicate ECGs) using Fridericia's correction of the QT interval for heart rate demonstrated a small degree of QTc prolongation in the citalopram and SCT treatment groups compared to placebo (3.7, 4.1, and 0.9, respectively).

It is not surprising that the clinical trial QTc mean changes from baseline analysis did not confirm the findings of study 98107. The clinical trials, with measurement of a single baseline and a single end of study ECG not timed to SCT dosing, were not designed to be sensitive to picking up changes in the QTc duration. In his discussion, Dr. Gan asserts that it is the use of an uncertain baseline QTc interval length to calculate the change from baseline that invalidates the findings of the sponsor's analysis. I would agree that the current thinking in 2002 on monitoring for drug effects on ECG encourages the measurement of multiple baseline ECGs with averaging of the various QTc interval durations. But this was not the standard approach at the time that the SCT studies were

conducted, and I don't believe that the sponsor can be faulted for not using multiple baseline QTc measurements. Rather, I believe that it is the lack of attention to the timing of the end of study ECG to correlate to the time of SCT dosing that has minimized the likelihood of identifying QTc prolongation should it exist.

Dr. Gan also asserts that the technical problem with the ECG machines described at length in his review compromises the integrity of the escitalopram development program. I agree that it is less than optimal to lose about 7% of the study ECGs; however, the error that was discovered (not holding down the "clear" button long enough between ECG measurements) appears to have been unintentional. Because DSI did not find problems with other components of the study data, I don't believe that the entire safety (or for that matter, efficacy) database is compromised.

There were no deaths, SAEs, or discontinuation due to adverse events reported during the development of SCT that were described as TdP or ventricular arrhythmia. Furthermore, there was only one SCT patient in the large controlled trials identified as having a QTc duration >500 msec. Hence we looked to the extensive postmarketing experience with racemate citalopram to inform us about the likelihood of TdP, ventricular arrhythmia, and/or QTc prolongation with the active enantiomer, SCT.

A review of the isolated citalopram overdose cases suggests that at elevated serum levels, citalopram is capable of prolonging the QT/QTc interval. The overdose TdP case described above is harder to interpret because of potential confounding by the patient's comorbidities and the concurrent ingestion of other substances, but the role of citalopram in the TdP can not be entirely ruled out. At therapeutic doses, several cases suggested citalopram-related QT or QTc prolongation. Most therapeutic dose cases describing TdP associated with citalopram use appeared to be confounded; however, although case **S01-DEN-01616-01**.was not fully detailed, it did not describe an obvious confounding factor Ultimately, because of the QTc prolongation signal from the clinical pharmacology study, and the appearance of QTc prolongation cases in postmarketing experience with citalopram, it is difficult to rule out the potential contributory effect of citalopram in TdP in a patient who already is at risk (because of hypokalemia, a concomitant QT prolonging drug, or preexisting cardiovascular disease).

The SCT labeling (as well as the citalopram labeling) should be amended to address the potential for SCT to induce modest QTc prolongation as reflected in the clinical pharmacology study and the postmarketing cases.

5 Labeling recommendations

Precautions

QTc Prolongation

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Draft Labeling
(not releasable

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Appendix I Summary Case Tables from Dr. Gan's Review[4]

Table 1 Forest reports
Table 2 MedWatch reports
Table 3 Lundbeck reports

Table 1. Reported Cases, The Forest Laboratories' Safety Database: 7/00-11/01

Case Code	Age	Sex	Date of Event	Reporter	Diagnosis	Dosage	Duration	Outcome	History
S00-UKI-01907-01	58	f	10/12/00	MD	VT	20 mg qd	1 day	hospitalization	Cardiovascular disease; HTN
L01-USA-01339-01	21	f	unk	MD publication	QTc +	400 mg overdose	unk	hospitalization	none
S01-USA-01623-01	unk	m	8/9/01	MD	QT + MI	200 pills	once	hospitalization	Suicide attempt
S00-USA-01913-01	unk	unk	unk	MD	QT + Death	unk	unk	Death?	unk
S01-USA-00206-01	42	f	2/8/01	Medical examiner	Death	unk	unk	death	asthma
S01-NOR-00229-01	24	f	?/?/00	MD	QTc + Torsade	30 mg qd	unk	Life threatening	unk
S01-GER-01168-01	unk	f	?/?/01	MD?	Torsade Syncope No QT +	20 mg qd	60 days	Other???	CAD
S01-FRA-00062-01	51	f	10/28/99	MD	QTc + Torsade	20 mg qd	unk	Life threatening	Alcoholic
S01-DEN-01616-01	44	f	5/12/01	MD	Torsade	20 mg qd	60 days	hospitalization	no
S01-USA-00268-01	42	f	8/7/00	MD	Torsade VT QT +	40 mg 550 mg ??	unk	Life-threatening hospitalization	Cardiac arrhythmia Hepatitis c Drug abuse
S00-UKI-01202-01	76	f	unk	MD	QT + VT	20 mg qd	90 days	hospitalization	CHF
S00-USA-01487-01	unk elderly	f	unk	MD	VT VF	20 mg qd	unk	hospitalization	CAD Implantable defibrillator
S01-USA-02093-01	62	f	8/2/01	MD	QTc + Syncope	20 mg qd	21 days	unk	COPD
S01-FIN-01644-01	23	m	6/30/01	MD?	Seizure (3min) QTc +	40mg 20 mg	7 days	Hospitalization	Anorexia nervosa 1995
S01-SWE-0052701	47	f	2/26/01	MD	QT+ Syncope	20 mg qd	Unk to 2/26/01	hospitalization	no
S01-USA-00543-01	unk	unk	unk	MD	QT +	unk	unk	unk	unk
S02-USA-01458-01	unk	unk	unk	MD	QT +	unk	unk	unk	unk
S00GER-01018-01	unk	m	6/19/00	MD?	QTc +	40 mg qd	unk	hospitalization	RBBB & on meds

[4] I have made some modifications to Dr. Gan's tables. In all cases, I went back to the original case narrative to determine if the reporter described "QT" or "QTc" prolongation. If the QT or QTc interval was not described in the narrative by the reporter, then there is no mention of QT in the "Diagnosis" field in the table. In some cases I added additional information. In Table 2, I altered the order of the patient entries to correspond to the text of this review.

Unk: unknown f:female m: male MD: medical doctor QT +: QT or QTc prolongation VT: ventricular tachycardia VA: ventricular arrhythmia

Table 2. Reported Cases not included in the sponsor's submission, MedWatch Database, July 1998 through April 30,2002

Case Code	Age	Sex	Date of Event	Reporter	Diagnosis	Dosage	Duration	Outcome	History
A029665	23	f	6/15/00	PA	QTc + PSVT	50 mg	90 days	Required intervention to prevent permanent impairment or damage	unk
2001UW-04122	unk	f	4/?/01	MD	VT QT+	unk	unk	hospitalization	QT+
S02-USA-00185-01	51	f	?/?/01	MD	QTc + syncope	40	unk	hospitalization	QT+
S02-USA-00153-01	70	f	12/27/01	MD	QT +	40mgqd 60mgqd	3 years 3 days	hospitalization	Suicide ideation
S02-UKI-00235-01	unk	f	12/8/01	MD	Seizure QT+	2240 mg once	once	hospitalization	none

Tables 3a-3c. Reported Cases, Post-Marketing review, An updated Survey of QT Prolongation and Torsade de Pointes Arrhythmia, Citalopram in Therapeutic Doses and Overdose. H. Lundbeck Report., Clinical trials through June 30, 2000

Table 3a. Citalopram therapeutic dose- torsades de pointes/ ventricular arrhythmia

Case Code	Age	Sex	Date of Event	Reporter	Diagnosis	Dosage	Duration	Outcome	History
DKLU0991409(0)	unk	f	unk	unk	TdP	unk	unk	hospitalization	none
DKLU0950329(0)	85	f	8/30/95	MD	TdP	40 mg	48 days	death	AF
DKLU0960542(0)	84	f	7/11/86	unk	TdP	40 mg qd	95 days	death	DM, AF
DKLU0906949(0)	69	f	unk	unk	TdP Syncope	20 mg	Unk	hospitalization	DM
DKLU0990565(0)	84	f	2/5/99	authority	TdP AF	10 mg qd	25 days	hospitalization	CHF
DKLU0991754(0)	85	f	9/19/99	unk	QTc + TdP	20 mg qd	115 days	hospitalization	DM
DKLU0950405(0)	62	m	10/5/95	unk	TdP QT +	20 mg	24 days	death	DM, RA
DKLU0960640(0)	25	f	8/23/94	unk	Syncope TdP	60 mg	93 days	hospitalization	Anorexia
DKLU0981158(0)	80	f	7/19/98	hospital	TdP	20 mg qd	49 days	hospitalization	HTN, AF
DKLU0990862(0)	65	m	4/9/99	unk	VT syncope	20 mg qd	unk	Life threaten	PVD CAD
DKLU0961160(0)	52	f	9/20/96	unk	QT + VF	20 mg qd	Unk	hospitalization	Kidney disease
DKLU0981678(0)	36	f	11/23/98	authority	QT + VF	10 mg qd	8 days	other	immunosuppression
DKLU0980606(0)	52	f	2/15/98	authority	polymorphic VT Syncope	20 mg qd	267 days	hospitalization	Syncope 1981
DKLU0991542(0)	89	F	7/24/99	Authority	VT convulsion	20 mg qd	unk	hospitalization	asthma

Table 3b. Citalopram therapeutic dose- QT prolongation

Case Code	Age	Sex	Date of Event	Reporter	Diagnosis	Dosage	Duration	Outcome	History
DKLU0970404(0)	77	f	unk	unk	QT + presyncope	40 mg qd	34 days	hospitalization	HTN
DKLU0996387(0)	56	F	7/1/99	Unk	QT + Syncope	30 mg qd	123 days	hospitalization	none
DKLU0200177	69	f	12/23/99	unk	Syncope QTc +	40 mg	unk	hospitalization	none
DKLU0991089(0)	79	f	unk	unk	QT + Unstable angina	20mg qd	14 days	hospitalization	CAD
DKLU0991651(0)	85	f	10/29/98	unk	QT + Unstable angina	10 mg qd	5 days	hospitalization	CAD HTN
DKLU0990710(0)	47	f	Unk	unk	QTc + bradycardia	40 mg qd	unk	hospitalization	Etoh abuse
DKLU0991162(0)	62	f	6/9/99	unk	QTc +	50mg qd	41 days	other	MI
DKLU0980361(0)	unk	f	11/20/97	unk	QTc +	40 mg	51 days	hospitalization	HTN, DM
DKLU0991392(0)	34	m	3/26/99	unk	QT +	30 mg qd	93 days	Unk	acne
DKLU1000737(0)	40	f	3/30/00	unk	QT +	10 mg qd	2 days	hospitalization	depression
DKLU0991813(0)	38	unk	unk	unk	QT +	20 mg qd	unk	unk	none
DKLU0980366(0)	unk	m	12/9/97	unk	QT +	20 mg qd	26 days	hospitalization	none
DKLU0980367(0)	unk	m	12/16/97	unk	QT +	40 mg qd	unk	hospitalization	none
DKLU0980368(0)	unk	f	12/9/97	unk	QT +	20 mg qd	unk	hospitalization	none
DKLU0980490(0)	unk	f	1/7/98	unk	QT +	20 mg qd	unk	unk	none
DKLU0980727(0)	unk	f	unk	unk	QT +	40 mg qd	unk	unk	none
DKLU0990171(0)	58	m	6/28/98	unk	QT +	40 mg qd	150 days	unk	none
DKLU0990445(0)	29	m	7/28/98	Hospital	QTc +	20mg qd	14 days	hospitalization	none
DKLU0991151(0)	64	F	6/17/99	Authority	QT +	Unk	Unk	hospitalization	Psych disorder
DKLU0991978(0)	Unk	f	unk	unk	QT +	20 mg qd	unk	other	none
DKLU1000001(0)	48	M	3/15/00	unk	QT +	40 mg	unk	hospitalization	none

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Table 3c. Citalopram- Overdose

Case Code	Age	Sex	Date of Event	Reporter	Diagnosis	Dosage	Duration	Outcome	History
DKLU0200028(2)	35	m	11/30/99	unk	QT +	overdose CIT only	once	hospitalization	None
DKLU1000032(0)	60	m	10/8/99	authority	QT +	overdose CIT only	once	other	HTN
DKLU0960100(0)	45	f	2/6/96	unk	QT +	Overdose CIT only	unk	hospitalization	depression
DKLU1000051(0)	14	f	4/10/00	unk	QT +	Overdose CIT only	once	hospitalization	Psych disorder
DKLU0970890(0)	45	f	unk	National Poison center	QT +	Overdose CIT only	unk	hospitalization	none
DKLU0970526(0)	26	f	1/17/97	unk	QTc + convulsion	Overdose CIT only	unk	hospitalization	none
DKLU0990881(0)	16	f	unk	unk	QT + convulsions	Overdose CIT only	1 time	hospitalization	none
DKLU0991467(2)	35	m	8/13/99	unk	QTc + convulsion	Overdose CIT only	1 day	hospitalization	Drug abuse
DKLU0991700(0)	18	F	9/21/98	unk	QT + convulsion	Overdose CIT only	1 day	hospitalization	suicidal
DKLU0960175(0)	22	f	unk	unk	QT + Convulsion	Overdose CIT only	unk	hospitalization	unk
DKLU1000039(1)	19	m	4/13/00	unk	QTc + seizure	Overdose CIT only	once	hospitalization	Drug abuse
DKLU0970893(0)	22	f	unk	National poison center	QT + bradycardia hypotension	Overdose CIT only	unk	hospitalization	none
DKLU0200342(0)	21	f	12/9/99	unk	QTc +	Overdose mixed	unk	unk	none
DKLU0970012(0)	27	f	9/20/96	unk	QT +	Overdose mixed	unk	hospitalization	Drug abuse
DKLU0970592(0)	25	f	4/16/97	Health Authority	QTc +	Overdose mixed	1 day	hospitalization	none
DKLU0970527(0)	44	m	12/1/96	unk	QTc +	Overdose mixed	1 day	hospitalization	Psych problem
DKLU0970525(0)	32	f	10/13/96	unk	QTc + convulsions	Overdose mixed	1 day	hospitalization	none
DKLU0990151(0)	26	f	1/20/99	unk	QT + seizure	Overdose mixed	1 day	hospitalization	bulimia
DKLU0970528(0)	42	m	10/8/94	unk	QTc + convulsions	Overdose mixed	1 day	hospitalization	depression
DKLU0991407(0)	23	f	8/1/99	unk	QT + convulsion	Overdose mixed	unk	unk	suicidal
DKLU0960180(0)	35	f	unk	unk	QT + convulsions	Overdose mixed	unk	hospitalization	unk
DKLU0970730(0)	47	m	8/10/97	unk	QTc + Torsade	Overdose mixed	unk	hospitalization	Cancer
DKLU0200255(0)	40	f	unk	unk	Convulsions VT	Overdose mixed	unk	hospitalization	migraine

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/s/

Judith Racoosin
7/29/02 02:32:45 PM
MEDICAL OFFICER

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